(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
11 January 2001 (11.01.2001)

PCT

(10) International Publication Number
WO 01/02005 A3

(51) International Patent Classification[7]: C12N 5/08, G01N 33/50, A61K 39/395, 39/005, 38/17, 35/14, 39/00, A61P 37/00, 33/06

(21) International Application Number: PCT/GB00/02546

(22) International Filing Date: 30 June 2000 (30.06.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
9915311.6 30 June 1999 (30.06.1999) GB

(71) Applicant *(for all designated States except US)*: **ISIS INNOVATION LTD.** [GB/GB]; Ewert House, Ewert Place, Summertown, Oxford OX2 7BZ (GB).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **ROBERTS, David, John** [GB/GB]; National Blood Service Oxford Centre, John Radcliffe Hospital, Headington, Oxford OX3 9DU (GB). **URBAN, Britta, Christina** [DE/GB]; Institute of Molecular Medicine, John Radcliffe Hospital, Headington, Oxford OX3 9DS (GB).

(74) Agent: **BOULT WADE TENNANT**; Verulam Gardens, 70 Gray's Inn Road, London WC1X 8BT (GB).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *With international search report.*

(88) Date of publication of the international search report:
5 July 2001

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/02005 A3

(54) Title: TREATMENT OF DENTRITIC CELLS FOR INDUCTION OF IMMUNE TOLERANCE

(57) Abstract: Methods and compositions for the induction of immune tolerance in mammalian antigen presenting cells such as dendritic cells, macrophages, monocytes and B-lymphocytes are described. Such methods and compositions involve the use of agonists of the cell surface receptors CD36, CD51, thrombospondin receptors and/or the β-integrins which when exposed to an antigen-presenting cell such as a dendritic cell are able to inhibit maturation therein. Thus, the cells' ability to promote an immune response is inhibited. Tolerance to a specific antigen can be induced in antigen-presenting cells by exposure to one or more of the aforesaid agonists and the antigen. Thus, cell preparations can be prepared for administration to humans where tolerance to a specific antigen or antigens needs to be induced, for example in the case of allograft or xenograft transplants or in autoimmune disease.

INTERNATIONAL SEARCH REPORT

Interi nal Application No
PCT/GB 00/02546

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12N5/08 G01N33/50 A61K39/395 A61K39/005 A61K38/17
A61K35/14 A61K39/00 A61P37/00 A61P33/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BIOSIS, MEDLINE, LIFESCIENCES, CHEM ABS Data, EMBASE, SCISEARCH

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 93 06848 A (BLOOD RES CENTER) 15 April 1993 (1993-04-15) the whole document ---	33-35, 38-41, 54-62, 75,76
X	MCCORMICK C J ET AL: "Intercellular adhesion molecule-1 and CD36 synergize to mediate adherence of Plasmodium falciparum-infected erythrocytes to cultured human microvascular endothelial cells." JOURNAL OF CLINICAL INVESTIGATION, vol. 100, no. 10, 15 November 1997 (1997-11-15), pages 2521-2529, XP000971964 the whole document --- -/--	54-62, 75,76

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 January 2001	25/01/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Teyssier, B

2

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/GB 00/02546

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 05191 A (UAB RESEARCH FOUNDATION) 23 February 1995 (1995-02-23) the whole document ---	33,34, 38-40, 43,44, 46, 49-51, 53,75, 104-107
X	WO 96 33736 A (AFFYMAX TECH NV ;BARUCH DROR I (US); HOWARD RUSSELL J (US); PASLOS) 31 October 1996 (1996-10-31) the whole document ---	33,34, 36, 38-40, 42,43, 46,47, 49-51, 53,75, 104-107
X	WO 90 15609 A (MED TAL INC) 27 December 1990 (1990-12-27) the whole document ---	108-111
A	ALBERT M L ET AL: "Immature dendritic cells phagocytose apoptotic cells via alpha V beta 5 and CD36, and cross-present antigens to cytotoxic T lymphocytes" JOURNAL OF EXPERIMENTAL MEDICINE, vol. 188, no. 7, 5 October 1998 (1998-10-05), pages 1359-1368, XP000906793 ---	
P,X	URBAN B C ET AL: "Modulation of dendritic cell maturation and function." TISSUE ANTIGENS, vol. 55, no. Supplement 1, 2000, page 61 XP000971966 7th Workshop and Conference on Human Leucocyte Differentiation Antigens; Harrogate, England; 20-24 June 2000 abstract I. 19 ---	1-115
P,X	URBAN B C ET AL: "Plasmodium falciparum-infected erythrocytes modulate the maturation of dendritic cells." NATURE, vol. 400, no. 6739, 1 July 1999 (1999-07-01), pages 73-77, XP002156922 the whole document -----	1-115

2

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-53, 77-115

Methods of treating antigen presenting cells, including dendritic cells, to induce immune tolerance; the resulting antigen presenting cells preparations and their use as a medicament.
Methods of identifiying agonists of CD36 or CD51; pharmaceutical compositions containing CD36 or CD51 agonists and their use as a medicament.

Methods of identifying agonists of a beta-integrin associated with CD51. Pharmaceutical composition containing a beta-integrin agonist and a CD51 agonist. Use of a beta-integrin agonist to induce tolerance in antigen presenting cells; tolerised cell composition.

Pharmaceutical composition containing a thrombospondin agonist. Use of a thrombospondin agonist to induce tolerance in antigen presenting cells; tolerised cell composition.

Pharmaceutical composition containing a negatively charged phospholipid. Use of a negatively charged phospholipid to induce tolerance in antigen presenting cells; tolerised cell composition.

2. Claims: 54-76

Methods of identifying a molecule capable of preventing the adherence of red blood cells infected with a malarial parasite to human dendritic cells; said molecule and pharmaceutical compositions comprising it.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

1/ Lack of clarity

Claims 1-3, 33, 37-39, 43, 46-50, 53, 73-76, 82-85, 87 and 115 relate to compounds, to pharmaceutical compositions comprising compounds or to methods using compounds in which said compounds are defined solely by reference to desirable characteristics or properties, namely the agonism of the cells surface receptors CD36 and/or CD51 or the prevention of the adherence of red blood cells infected with a malarial parasite to human dendritic cells. The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.
Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compounds by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible.
Consequently, the search has been carried out for those parts of the claims which appear to be clear, disclosed and supported, nametly namely, antibodies to CD36 and/or CD51 (as applicable), Pf-EMP-1, thrombospondin, fragments and derivatives of said antibodies and proteins, and negatively charged phospholipids, as mentioned in claims 4, 6-8, 34-36, 40-42, 44, 45, 51, 52 and 88.

2/ Inconsistencies in claims 9, 35-37 and 102-103

Claim 9 relates to "a method as claimed in any one of claims 40 to 47" while said claims 40-47 relate to compounds and compositions therof; claim 9 is therefore inconsistent. In view of the context of these claims, this International Search Authority assumed that claim 9 refers to claims 1-8.

Claims 35-36 and 37 relate to a composition as claimed in claim 20 and 19, respectively, while said claims 20 and 19 relate to a method of identifying ligands; claims 35-37 are therefore inconsistent. In view of the context of these claims, this International Search Authority assumed that claims 35-36 refer to claim 34 and that claim 37 refers to claim 33.

Claims 102-103 relate to "a preparation of cells obtainable by the the method as claimed in any one of claims 97 to 100" while claim 97 relates to a pharmaceutical composition of a beta-integrin. Claims 98-100 do relate to a method suitable to obtain a composition of claims 102-103. Consequentely, the part of claims 102-103 which relate to claim 97 was disregarded.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

...information on patent family members

Inter... nal Application No
PCT/GB 00/02546

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9306848 A	15-04-1993	AU 2795892 A	03-05-1993
		AU 2797892 A	03-05-1993
		AU 2861292 A	03-05-1993
		WO 9306849 A	15-04-1993
		WO 9306850 A	15-04-1993
WO 9505191 A	23-02-1995	AU 697624 B	15-10-1998
		AU 7565294 A	14-03-1995
		CA 2169360 A	23-02-1995
		EP 0716609 A	19-06-1996
		JP 9505555 T	03-06-1997
WO 9633736 A	31-10-1996	AU 5851296 A	18-11-1996
WO 9015609 A	27-12-1990	EP 0477270 A	01-04-1992
		US 5135922 A	04-08-1992
		US 5262406 A	16-11-1993